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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,063	WANDS ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *23,39-41,44-47 and 50-57* is/are pending in the application.

4a) Of the above claim(s) *45,47,52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23,39-41,44,46,50,51 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 24-38, 42, 43, 48 and 49 have been canceled. Claims 54-57 have been added. Claims 23, 39-41, 44-47 and 50-57 are pending. Claims 45, 47, 52 and 53 remain withdrawn from consideration. Claims 23, 39-41, 44, 46, 50, 51 and 54-57 are under consideration.

2. Applicant's request for a corrected filing receipt, filed May 7, 2002, is noted. The request will be forwarded to the appropriate PTO-official for processing.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. Claims 23, 44, 46, 50, 51, 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (WO 98/19691, cited in the previous Office action) as evidenced by the abstract of Ince et al (Hepatology, Oct. 1999, Vol. 30, No. 4, Part 2, Suppl., page 1398).

Claim 23 is drawn to a method of inhibiting tumor growth comprising identifying a mammal comprising an elevated level of a HAAH polypeptide compared to a normal non-neoplastic level of said peptide said HAAH polypeptide comprising SEQ ID NO:2, and administering to said mammal a compound which inhibits tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), said IRS-1 comprising an amino acid sequence of SEQ ID NO:5, wherein said compound is a dominant negative IRS-1 mutant comprising a mutation in a carboxyl-terminal SH2 binding motif of SEQ ID NO:5. Claim 44 embodies the method of claim 23 wherein said tumor is liver cancer. Claim 46 embodies the method of claim 23 wherein said tumor is hepatocellular carcinoma. Claims 50, 51, 54 and 55 embody the method of claim 23 wherein said mutant comprises a mutation at position 897, 1180, 613 and 942 of SEQ ID NO:5, respectively. Claim 56 embodies the method of claim 23, wherein said mutant comprises a mutation at position 897 and 1180 of SEQ ID NO:5. Claim 57 embodies the method of claim 23 wherein said mutant comprises a mutation at position 613 and 942 of SEQ ID NO:5.

Tanaka et al teach a method of eliminating or mitigating tumor growth in a mammal comprising administering a dominant-negative IRS-1 mutant comprising the carboxyl-terminal SH2 binding region of human IRS-1 (page 6, lines 3-14). Tanaka et al teach liver cancer as an

embodiment of a tumor (page 6, line 15). Tanaka et al teach that dominant-negative mutants of the invention are lacking a functional carboxyl terminus (page 8, lines 7-9). Tanaka et al teach that said mutants can be used to block the insulin-activated signal transduction pathway n a cell (page 14, lines 1-3).

Tanaka et al teach that carboxyl terminus comprises SH2 binding motifs at tyrosine residues 897, 1180, 613, and 942 which bind to Syp, Grb2, P13K and Nck, respectively. Tanaka et al teach that the tyrosines at residues 613 and 942 are the principal binding sites for the p85-subunit of phosphatidylinositol-3 kinase (PI3K) (page 2, lines 23-25). Tanaka et al teach that the dominant negative mutant of the invention have altered conformation of the biding motifs due to amino acid substitution which renders said motifs unable to bind to their specific receptors (page 8, lines 19-31). Tanaka et al identifies the functional domains required for the transforming activity of IRS-1 as residing in the 897 SH@ motif and the 1180 SH2 motif (page 3, lines 23-26).

Tanaka et al teach that dominant-negative mutants of the invention can be used to eliminate or mitigate a malignant phenotype, such as liver cancer, in which hyperactivity of IRS-1 is known to play a causative role (page 6, lines 11-17). Tanaka et al teach that the dominant-negative mutants of the invention block the insulin-activated signal transduction pathway by inhibiting tyrosine phosphorylation of endogenous human IRS-1 (page 8, lines 16-19). Tanaka et al do not specifically teach IRS-1 would comprise SEQ ID NO:5, however, the human IRS-1 protein taught by Tanaka et al would inherently comprise SEQ ID NO:5. Tanaka et al do not teach the identification of a mammal comprising an elevated level of HAAH polypeptide relative to a normal non-neoplastic level.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify a mammal with liver cancer wherein said liver cancer was associated with hyperactivity of IRS-1, and treat said mammal with dominant negative mutants of IRS-1 , wherein said mutants comprised amino acid substitutions at residues 897, 1180, 613 and 942 which altered the conformation of the SH2 binding motif as taught by Tanaka et al. One of ordinary skill in the art would have been motivated to do so in order to identify patients which would benefit from the antagonism of the IRS-1 signal transduction pathway. Further, based on the teachings of Tanaka et al it would be obvious to construct double mutants

having amino acid substitutions at residues 613 and 942, because Tanaka et al identifies both residues as important for the binding to the PI3K receptor. Thus, a double mutant having substitutions at both tyrosine residues 613 and 942 would not be able to bind to the PI3K receptor. Further, based on the teachings of Tanaka et al, .it would be obvious to construct the double mutant having amino acid substitutions at residues 897 and 1180 because Tanaka et al teach that the motifs comprising said residues are the functional domains responsible for the transforming activity of IRS-1. One of skill in the art would be motivated to do so decrease the IRS-1 mediated downstream signaling and transforming activity. The abstract of Ince et al teaches that HAAH gene expression was associated with the activation of the IRS-1 signal transduction pathway (lines 12-16). Thus, it would be inherent in the identification of patients exhibiting hyperactivity of IRS-1 that said patients would comprise elevated levels of HAAH polypeptide.

5. Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al (WO 98/56387, cited in the previous Office action)in view of Rogan et al (International Journal of Oncology, 1999, Vol. 15, pp. 589-594, cited in a previous Office action) and Tanaka et al (WO 98/19691, cited in the previous Office action) as evidenced by the abstract of Ince et al (Hepatology, Oct. 1999, Vol. 30, No. 4, Part 2, Suppl., page 1398).

Claim 39 is drawn to a method of inhibiting tumor growth in a mammal comprising identifying a mammal comprising an elevated level of an HAAH polypeptide compared to a normal non-neoplastic level, said HAAH polypeptide comprising the amino acid sequence of SEQ ID NO:2, and administering to said mammal a compound which inhibits tyrosine phosphorylation of an insulin-receptor substrate-1 (IRS-1), said IRS-1 comprising SEQ ID NO:5, wherein said compound is a vitamin D analogue. Claim 40 embodies the method of claim 39 wherein said compound is EB1089.

Morris et al teach a method for inhibiting liver cancer comprising the administration of a vitamin D compound, metabolite or analogue thereof (abstract and page 4, lines 28-30). Morris et al do not teach that said vitamin D compound, precursor, metabolite or analogue thereof inhibits the tyrosine phosphorylation of the insulin receptor substrate-1 of SEQ ID NO:5, or a

method comprising the identification of a mammal comprising a elevated level of HAAH polypeptide compared to a normal non-neoplastic level.

Rogan et al teach that the vitamin-D analogue EB1089 inhibits the tyrosine phosphorylation of IRS-1 (abstract, line 12-15) and suggest the administration of vitamin D analogue for the treatment of cancer(page 593, last sentence of "Discussion").

Tanaka et al teach a method for eliminating or mitigating tumor growth, specifically liver cancer, by the administration of a dominant negative mutant of IRS-1 (page 6, lines 3-14). Tanaka et al teach that the dominant-negative mutants of the invention block the insulin-activated signal transduction pathway by inhibiting tyrosine phosphorylation of endogenous human IRS-1 (page 8, lines 16-19). Tanaka et al do not specifically disclose the sequence of SEQ ID NO:5 , but said sequence would be inherent in human IRS-1. Tanaka et al teach that the dominant negative mutants can be used to reverse a malignant phenotype of mammalian tumor in which hyperactivity of IRS-1 is known to be a causative role (page 6, lines 11-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify a mammal with liver cancer wherein said liver cancer was associated with hyperactivity of IRS-1, and treat said mammal with the vitamin D analogue EB1089. One of skill in the art would be motivated to do so to identify patients which would benefit from reduction of the activity of IRS-1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rogan et al on the interference with the tyrosine phosphorylation of IRS-1 by EB1089, and the teachings of Tanaka e al on the therapeutic administration of dominant-negative proteins which inhibit IRS-1-mediated signal transduction by antagonizing the phosphorylation of endogenous IRS-1. The abstract of Ince et al teaches that HAAH gene expression was associated with the activation of the IRS-1 signal transduction pathway (lines 12-16). Thus, it would be inherent in the identification of patients exhibiting hyperactivity of IRS-1 that said patients would comprise elevated levels of HAAH polypeptide.

6. Claims 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al (WO 98/56387, cited in the previous Office action) and Rogan et al (International Journal of Oncology, 1999, Vol. 15, pp. 589-594, cited in a previous Office action) and Tanaka et al (WO

98/19691, cited in the previous Office action) and the abstract of Ince et al (Hepatology, Oct. 1999, Vol. 30, No. 4, Part 2, Suppl., page 1398).in view of Ogawa et al (Molecular and Cellular Biochemistry, 1998, Vol. 182, pp. 13-22, cited in the previous Office action).

The specific embodiments of claims 39 and 40 are set forth above. Claim 41 is drawn to a method of inhibiting tumor growth in a mammal comprising identifying a mammal comprising an elevated level of a HAAH polypeptide and administering to said mammal a compound which inhibits tyrosine phosphorylation of insulin receptors substrate-1 (IRS-1) wherein said compound is Wortmannin and wherein HAAH polypeptide comprises SEQ ID NO:2 and IRS-1 comprises SEQ ID NO:5. .

The teachings of Morris et al, Rogan et al, Tanaka et al and the abstract of Ince et al which render claims 39 and 40 obvious are set forth above. Neither Morris et al, Rogan et al, Tanaka et al nor the abstract of Ince et al teach the administration of Wortmannin to inhibit the tyrosine phosphorylation of IRS-1.

Ogawa et al teach that Wortmannin decreases the activity and production of PI-3, 4 and 5 induced by insulin and results in the inhibition of the signal from IRS-1 leading to protein synthesis and mitogenesis and specifically inhibits the catalytic activity of p110 (page 16, first column, first full paragraph, and page 18, Figure 5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute Wortmannin for the vitamin-D analogue EB1089 in the method of treatment rendered obvious by the combination of Morris et al, Rogan et al, Tanaka et al and the abstract of Ince et al.. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Ogawa et al on the inhibition of IRS-1 signal transduction , and the inhibition of mitogenesis induced by Wortmannin.

7. All other rejections and objections as set forth in Paper No. 14 are withdrawn in light of applicants amendments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/24/03